HIV exposed uninfected South African infants experience greater severity but not frequency of common infectious diseases than HIV unexposed uninfected infants

Amy L. Slogrove, Mark F. Cotton, Tobi R. Kollman, David P. Speert, Monika Esser, Joel Singer, Julie A. Bettinger

HIV Paediatrics Workshop, Vancouver, July 2015

Introduction

- HIV exposed uninfected (HEU) infants in Africa may experience greater infectious morbidity than HIV unexposed uninfected (HUU) infants

- HEU infant infectious morbidity pathways

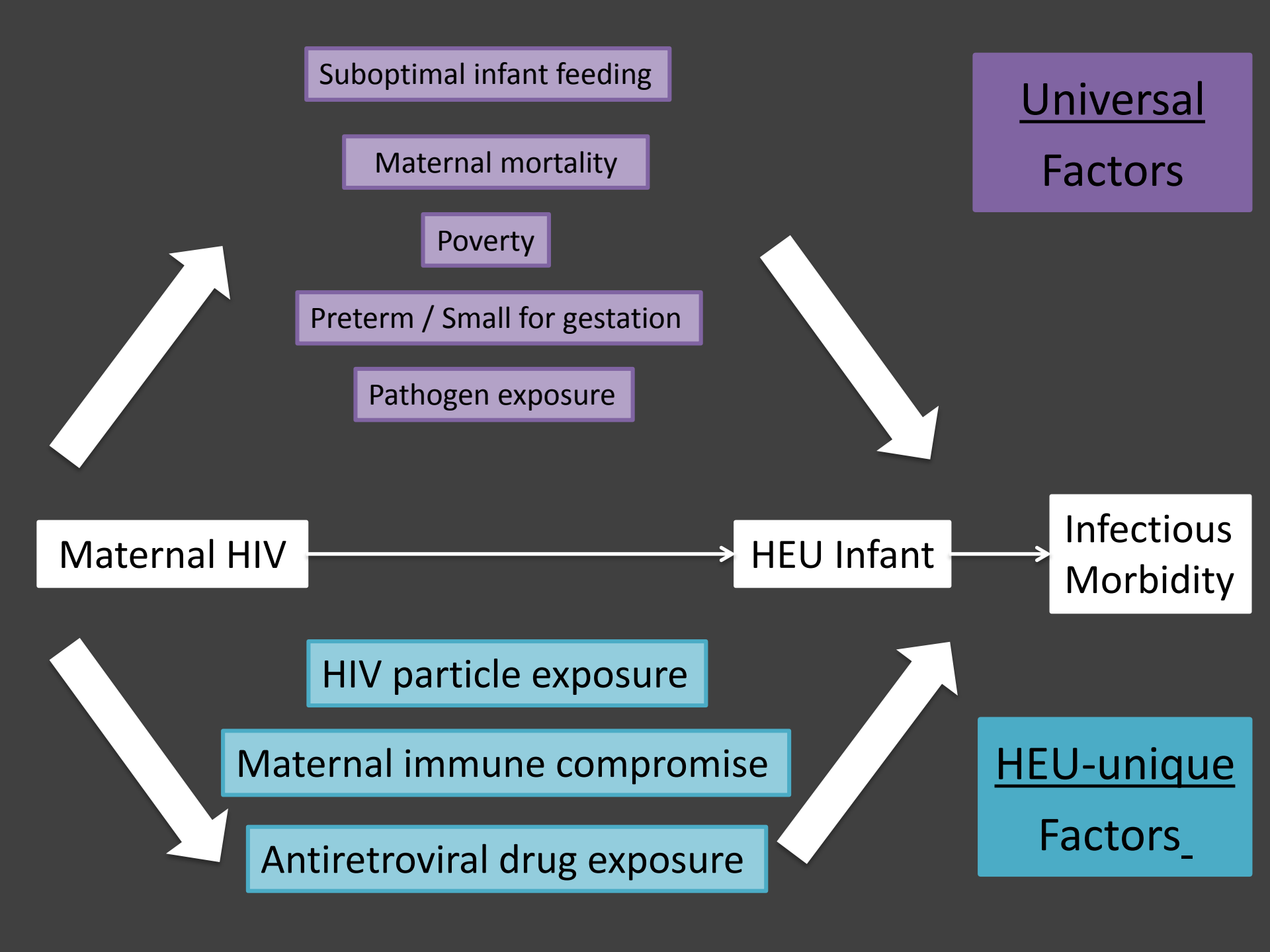
  Universal infant risk factors:

  - Infant feeding, maternal mortality, poverty, preterm birth/small for gestational age, infectious pathogen exposure

  HEU-unique exposures:

  - HIV viral particle exposure, maternal immune compromise, ARVs

Marinda 2007, Shapiro 2007, Koyanagi 2011, Kelly 2014, von Mollendorf 2015


Suboptimal infant feeding
Maternal mortality
Poverty
Preterm / Small for gestation
Pathogen exposure
Universal Factors
Maternal HIV
HEU Infant
Infectious Morbidity
HIV particle exposure
Maternal immune compromise
Antiretroviral drug exposure
HEU-unique Factors

Infectious morbidity severity

- ZVITAMBO (N = 12 000+) & Mashi (N = 671)
  - greater relative difference in mortality than hospitalization
- Pneumonia treatment response at 48 hours
  - KZN (N = 116) & Botswana (N = 217)
  - HEU infants greater odds of empiric treatment failure
- Drakenstein Child Health Study (N= 697)
  - All pneumonia aRR 1.6 (95% CI 1.0, 2.6) HEU
  - Severe pneumonia aRR 4.0 (95% CI 1.5, 10.8) HEU

Marinda 2007, Koyanagi 2011; Shapiro 2007; McNally 2007; Kelly 2014; Le Roux 2015

Objectives

Primary:

To determine whether HIV exposed uninfected (HEU) infants have a greater probability of infectious cause hospitalization or death in the first 6 months of life, compared to HIV unexposed uninfected (HUU) infants from a single community, after controlling for differences in infant feeding

Secondary:

To determine whether HEU infants have a greater probability of severe or very severe infectious cause hospitalization or death than HUU infants

Definitions

Determinants

- Primary: HIV exposure (HEU / HUU)
  - Maternal HIV-infection status confirmed on all mothers at 2 weeks postnatal
  - Infant HIV-infection excluded at 6 weeks (HEU)and 6 months (HEU & HUU)
- Secondary: breastfeeding
  - Any / none at 2 weeks or 6 months

Outcomes

- **Primary**: at least 1 infectious cause hospitalization or death
- **Secondary:** at least 1 severe or very severe infectious cause hospitalization or death

- Study specific case-definitions:
  - Type and grade (mild-moderate, severe, very severe)
  - Based on WHO IMCI & SA child health management guidelines

Study Design & Setting

- Prospective cohort study in Kraaifontein, South Africa
- HIV-infected and uninfected mothers & their newborns
- Midwife obstetric unit – low risk term deliveries
- Enrolled July 2012 to June 2013
- Followed-up to 6 months
  - 4 visits

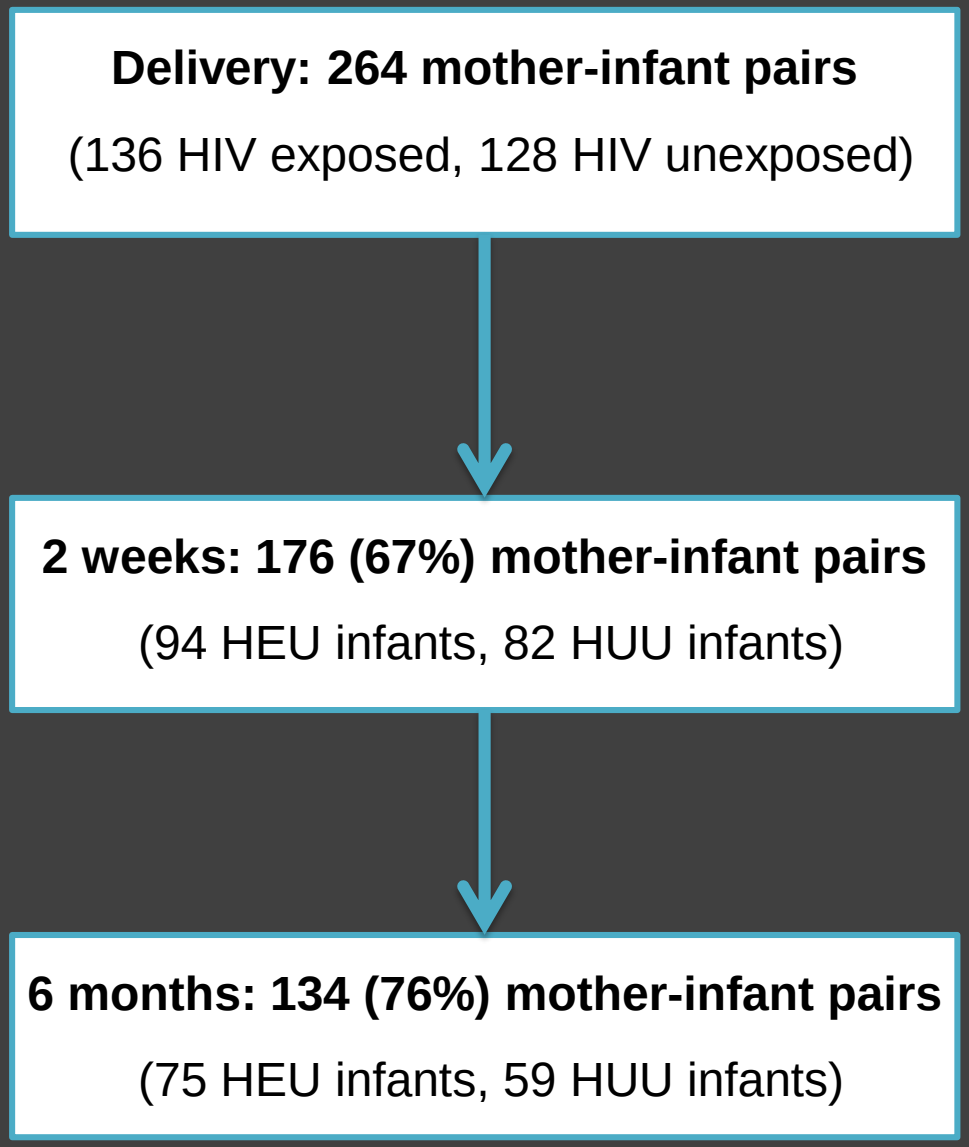
Control for confounding in study design

- Socio-economic circumstances
  - 4 well-defined low socio-economic neighbourhoods
- Maternal habits – alcohol, smoking, drug use
  - Mothers frequency matched on race/ethnicity
- Maternal health
  - Low risk obstetric histories
  - No major medical comorbidities
- Birth outcomes
  - $\geq$ 36 weeks gestation, $\geq$ 2000g
- Seasonality of common childhood infections
  - HEU and HUU infants matched within 30 days of birth

Outcome Determination

- Linkage with provincial electronic hospital administration system and mortality registry
  - Identify occurrence of hospitalization or death
  - All infants including those lost to face-to-face follow-up
- Hospital record abstraction according to a standardized abstraction source document, excluding all HIV exposure information
- 2 paediatricians independently graded and classified all hospitalization events according to the study-specific case-definitions

Results


Delivery: 264 mother-infant pairs
(136 HIV exposed, 128 HIV unexposed)
2 weeks: 176 (67%) mother-infant pairs
(94 HEU infants, 82 HUU infants)
6 months: 134 (76%) mother-infant pairs
(75 HEU infants, 59 HUU infants)

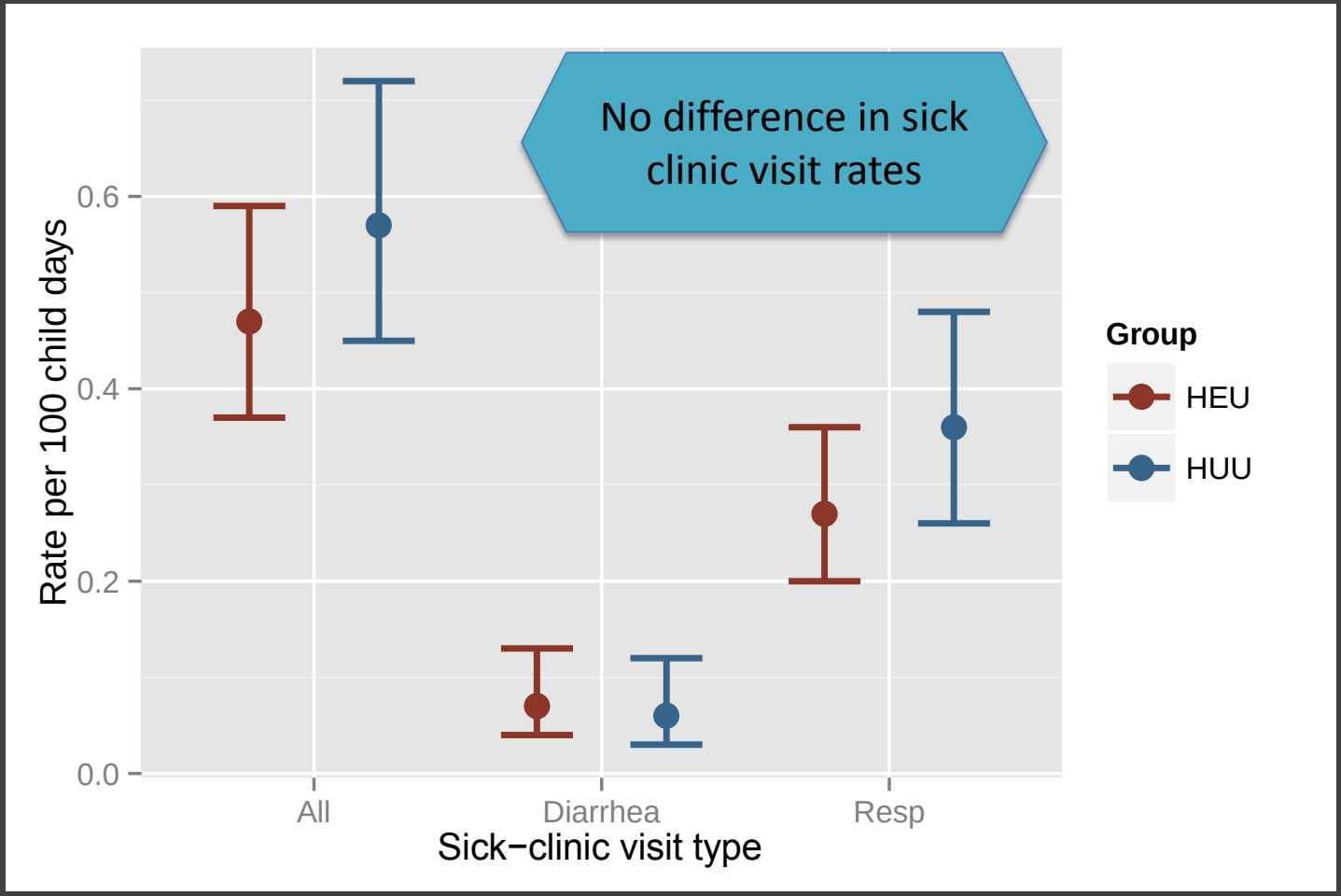
Maternal Characteristics

- Demographic
  - HIV-infected mothers significantly older than HIV-uninfected mothers (median 27.8 vs. 24.7 years, $p<0.008$)
  - No difference in race, marital status, education, income
- Obstetric
  - Equivalent antenatal care received
  - No major obstetric morbidities
- Health
  - Similar postnatal BMI (median 26.6 vs. 26.5 kg/m^2)
  - Delivery CD4 count lower in HIV-infected than HIV-uninfected mothers (343 cells/μl vs. 467 cells/μl, $p <0.001$)

Infant Characteristics

- No difference between HEU and HUU infants in
  - Birth weight (mean 3118g vs. 3231g, p = 0.07)
  - Gestational age (mean 38.7 vs. 39.1 weeks, p = 0.06)
  - Immunization up take (93% vs. 91% complete at 6 months)
- Fewer HEU infants breastfed than HUU infants
  - Never breastfed: two thirds of HEU, 1 HUU infant
  - 6 months: 85% of HEU and 32% of HUU not breastfeeding
- Breastfed infants
  - median duration 112 days (IQR 56, 194)
  - no difference between HEU and HUU

Sick clinic visit rates



Primary Outcome Events

- 27 infants had a primary outcome event
  - 17 HEU infants hospitalized once
  - 10 HUU infants (8 hospitalized once, 1 hospitalized twice, 1 death)
- 18% of HEU and 12% of HUU
- Unadjusted risk ratio

  1.48 (95% CI 0.72, 3.06)

Infectious Cause Hospitalizations

	Total (N=176)	HEU (N=94)	HUU (N=82)
Grade			
Mild-moderate (%)	3(1.7)	2(2.1)	1(1.2)
Severe (%)	9(5.1)	5(5.3)	4(4.9)
Very severe (%)	14(8.0)	10(10.6)	4(4.9)
Type			
Respiratory (%)	17(9.7)	10(10.06)	7(8.5)
Diarrhea*(%)	**9(5.1)**	**8(8.5)**	**1(1.2)**
Other#(%)	5(2.8)	4(4.3)	1(1.2)

* P = 0.04

#Other events: 3 HEU presumed neonatal sepsis, 1 HEU post-neonatal *Shigella sonnei* septicemia, 1 HUU uncomplicated neonatal conjunctivitis

The effect of HIV exposure on infectious morbidity

At least one infectious cause hospitalization or death in HEU relative to HUU infants

(adjusted for maternal age and any breastfeeding at 6 months)

	aOR	95% CI
All	1.47	0.54, 4.25
Severe	1.31	0.45, 4.02
Very severe	1.37	0.39, 5.57

Stratified Analysis:
No breastfeeding

2 weeks	Models not possible (single HUU infant not breastfed at 2 weeks)

6 months

Outcome	aOR	95% CI
All	1.34	0.42, 5.19
Severe	1.06	0.32, 4.18
Very severe	1.04	0.27, 5.09

All models adjusted for maternal age

Stratified Analysis: Any breastfeeding

2 weeks

Outcome	aOR	95% CI
All	1.96	0.59, 6.22
Severe	2.16	0.64, 7.01
Very severe	**4.21**	**1.00, 19.22**

6 months

Outcome	aOR	95% CI
All	1.82	0.24, 10.2
Severe	2.07	0.27, 12.0
Very severe	3.75	0.14, 6.00

All models adjusted for maternal age

Summary

- In term infants born to mothers without major obstetric or medical morbidities, in similar socioeconomic and household circumstances and with an equivalent frequency of infant sick-clinic visits
  - There is no evidence of a difference in infectious morbidity comparing HEU and HUU infants that stop breastfeeding before 6 months of age
  - Breastfed HEU infants vs. breastfed HUU infants had a 4 X greater probability of very severe infectious morbidity

Limitations

- Sample size & attrition
- Residual confounding by infant feeding and socioeconomic circumstances

Strengths

- Appropriate HIV unexposed comparison group
- Outcome severity grading

Conclusion

- HEU and HUU infants may differ in the severity but not in the incidence of common childhood infections experienced
- HEU-unique exposures may mediate some of the risk of HEU infant infectious morbidity

Acknowledgements

Co-Investigators:
David Speert
Monika Esser
Tobias Kollman
Mark Cotton

PhD students:
Gareth Mercer
Moleen Zunza
Cilla Springer
Kenneth Hammond

Sub-study collaborators:
Emma Kalk
Monique Andersson

PhD Committee:
Julie Bettinger
Joel Singer
Mark Cotton
Ying MacNab

HEU Pilot Study team
KID-CRU team
Vaccine Evaluation Center
SU - Paediatrics & Child Health
UBC – School of Population & Public Health

Funders:
UBC PWIAS
CIHR Canada Hope Fellowship
CTN International Fellowship
SA National Health Scholarship

Study Participants